Duodenal Mucosal Resurfacing Improves Glycemic, Lipid and Hepatic Fat Fraction Measures in Type 2 Diabetes

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Introduction

- Duodenal Mucosal Resurfacing (DMR) is currently being investigated as a treatment for insulin resistant metabolic disease including Type 2 diabetes (T2D).[1-4]
- Data from the recent multicenter, single-arm Revita-1 study in T2D patients demonstrated sustained reductions through 12 months in HbA1c, fasting plasma glucose (FPG), Homeostasis Model Assessment index (HOMA-IR), and liver transaminase levels.[4]

Objective

- Revita-2 clinical trial (NCT02879383) is a blinded, sham controlled study designed to evaluate the effects of DMR on glycemic and hepatic parameters in T2D, specifically HbA1c and fat fraction in the liver through magnetic resonance imaging-proton density fat fraction (MRI-PDFF).
- Trial design involves an initial open label phase in which the study sites familiarize themselves with the intervention procedure, followed by a randomized phase of the protocol. Sites were required to conduct 1-5 (open-label) training cases.
- We report data from the open label case cohort comprising of 24 subjects who had complete data out to 12 weeks. 20 of 24 subjects underwent liver MRI-PDFF, and we report hepatic MRI-PDFF data from the 17 of 20 subjects who had excess liver fat (defined as MRI-PDFF >5% at baseline).

Methods

- Eligible subjects participated in 4 week run-in period to confirm stable baseline glycemia, as well as medicational and nutritional compliance.
- Metabolic data (e.g. HbA1c, lipid and hepatic parameters) was collected at baseline and 12 weeks.
- Liver MRI-PDFF was performed at selected sites at baseline and 12 weeks with Philips Ingenia 3.0T systems (three sites) and GE Discovery 3.0T/Optima 1.5T systems (two sites) in a single breath-hold (<20 seconds), with 6 mm slice thickness and 2-2.5 mm isotropic in plane resolution. For each scan, nine region-of-interest (ROIs) were sited in each Coinaud liver segment with change in mean ROI liver fat fraction (%) recorded for each subject.
- All subjects enrolled in the open-label cohort were treated with the DMR procedure and will be followed per protocol for 48 weeks.

Key Inclusion Criteria:

- Aged 28-75 years
- HbA1c 7.5-10.0%
- BMI 24-40 kg/m2
- Fasting insulin >7 uIU/ mL
- Sub-optimally controlled on one or more oral anti-diabetic medication

Key Exclusion Criteria:

- Diagnosed with Type 1 diabetes or with a history of ketoacidosis
- Current use of Insulin or GLP-1 drugs
- Hypoglycemia unawareness or a history of severe hypoglycemia
- Known autoimmune disease, as evidenced by a positive Anti-GAD test,
- Active *H. pylori* infection
- Previous GI surgery that could affect the ability to treat the duodenum
- History of chronic or acute pancreatitis
- Known active hepatitis or active liver disease

Endoscopic Procedure:

- Subjects received DMR treatment under either deep sedation or general anaesthesia per local site preference.
- Catheter (followed by an endoscope for visualization) was inserted trans-orally over a stiff guidewire into the duodenum to a location just distal to the papilla (Figure 1A and 1B).
- Duodenum underwent circumferential hydrothermal ablation after mucosal lifting at five sequential locations between the papilla and ligament of Treitz (Figure 1C).

Figure 1A. REVITA™ Catheter

Figure 1B. Schematic of DMR

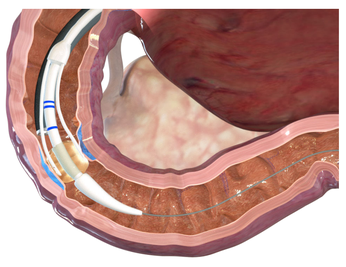
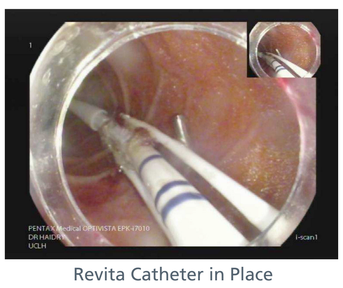
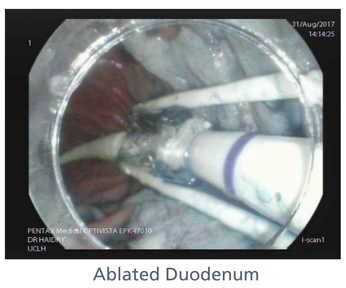


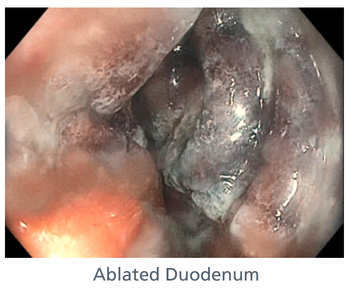
Figure 1C. DMR Images



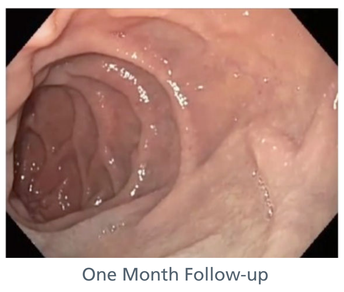
Revita Catheter in Place



Ablated Duodenum



Ablated Duodenum



One Month Follow-up

Results

Demographics

- Initial data from the open-label cohort are presented for 24 subjects through 3 months (12 weeks).
- Subjects enrolled had a mean age of 58 yrs with a mean duration of T2D of 8 yrs. All but one subject was receiving metformin. Two patients (8%) were receiving monotherapy and of those on more than one oral agent, the majority (63%) were taking a sulfonylurea.
- 20 of 24 subjects underwent liver MRI-PDFF at baseline and 12 weeks. 17 of the 20 (85%) had excess liver fat (defined as MRI-PDFF >5% at baseline).

Table 1. Subject Demographics and Baseline Characteristics

Subject Characteristics	Baseline (n=24)
Age, years (range)	58 (43-69)
Gender, n (%)	
Female	7 (29)
Male	17 (71)
Duration of T2D, years (range)	8 (0.4 -17)
Weight (kg)	89.7 (1.9)
BMI (kg/m²)	31.6 (3.0)
Oral antidiabetic medications	
Metformin*, n (%)	23 (96)
Sulfonylurea, n (%)	15 (63)
DPP-4 inhibitor*, n (%)	9 (38)
SGLT-2 inhibitor, n (%)	5 (21)

Values are mean (SD) unless otherwise noted. BMI: Body Mass Index; * includes combination agents counted in each category

Procedural Metrics

- Key procedural metrics including procedure time, defined as catheter in to catheter out duration, and number of ablations completed vs. intended are shown in Table 2.

Table 2. Key Procedural Metrics

Metric	Data
Median procedure time (Inter-quartile range), min	45 (18)
Number of completed/intended ablations*, n (%)	116/120 (97%)

*Five intended ablations per protocol, n=24 subjects

Efficacy

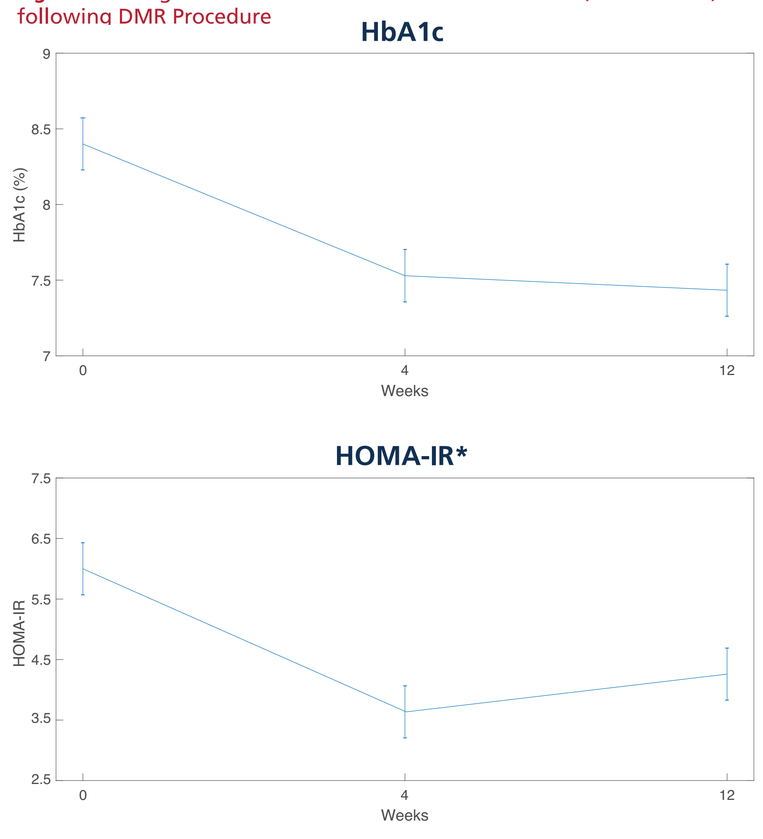
- Compared to baseline, significant improvement in all parameters of HbA1c and other metabolic parameters were observed (Table 3).

Table 3. Baseline and 12 Week Metabolic and Glycemic Values

Indices	Baseline	12 weeks	P value
HbA1c (%)	8.4 ± 0.2	7.4 ± 0.2	= 0.001
Fasting Plasma Insulin** (uIU/ml)	13.6 ± 1.8	9.8 ± 1.1	< 0.05
Fasting C-peptide (ng/ml)	3.2 ± 0.3	2.7 ± 0.2	= 0.01
Fasting Triglycerides (mg/dl)	209.0 ± 32.0	150.0 ± 20.0	< 0.01
Fasting HDL (mg/dl)	45.7 ± 2.8	49.2 ± 3.2	< 0.05
Ferritin* (ng/ml)	90.8 ± 16.6	69.4 ± 15.5	< 0.01
Alanine Aminotransferase (U/L)	35.8 ± 4.1	27.2 ± 2.4	< 0.001
HOMA-IR**	6.0 ± 0.7	4.1 ± 0.6	= 0.01
Body Weight (kg)	89.7 ± 1.9	86.6 ± 2.0	< 0.01

Values are all mean (±SEM); n = 24 except where indicated; * n=23,** n=22

Figure 2. Changes over 12 weeks in HbA1c and HOMA-IR (mean ± SEM) following DMR Procedure



Values are all mean (±SEM); n = 24 except where indicated; * n=22

Figure 3A. Liver Mean MRI-PDFF (absolute and relative change at 12 Weeks) following DMR Procedure (n=17)

- Liver MRI-PDFF data from a subset of 17 subjects, whom had excess baseline liver fat by MRI-PDFF (i.e >5%) revealed lowering of absolute (-7.0%±1.6, p<0.001) and relative (-35.8%±7.8, p<0.001) fat fraction in the liver.

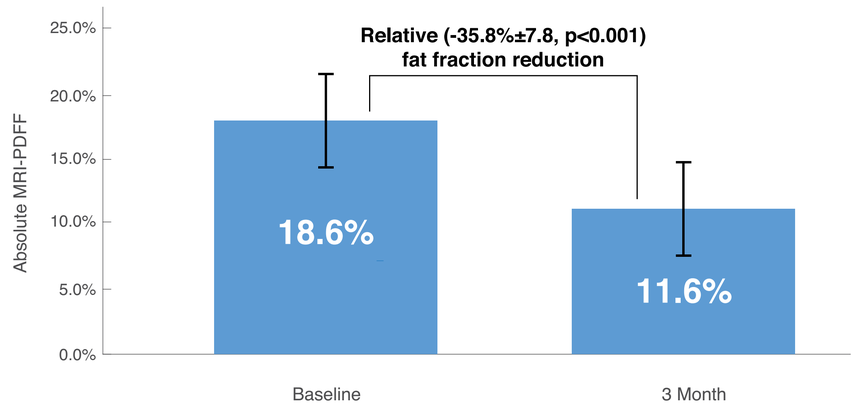
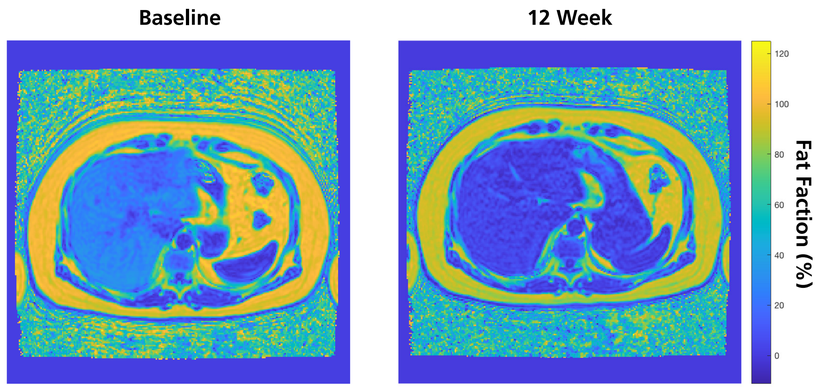


Figure 3B. Liver MRI-PDFF Imaging (from a single subject) following DMR Procedure



Baseline (left) and 12 Week (right) post treatment PDFF images from a single subject. Reduction in signal in the liver reflects a reduction in the PDFF following treatment. On colored PDFF images, a darker blue is indicative of a reduction in Hepatic fat content.

Safety

- Mild gastro-intestinal symptoms immediately post-procedure were the most commonly reported adverse event (AE), including abdominal pain, constipation, diarrhea, and dyspepsia.
- No device or procedure related serious AEs were reported.
- No unanticipated adverse device effects were reported.

Summary

- Glycemic and metabolic data demonstrate that DMR lowers HbA1c by 1.0% within 3 months from a baseline of 8.4% along with significant reductions in HOMA-IR and fasting C-peptide.
- Lipid parameters were improved with significant reductions in triglycerides and increases in fasting HDL.
- Hepatic parameters were improved with significant reductions in Alanine Aminotransferase (ALT) and Ferritin. MRI-PDFF of the liver indicates a significant absolute reduction of liver fat by 7.0%and a significant relative reduction of 35.8%.
- The DMR procedure was safely implemented across study sites and was well tolerated with mostly mild and transient GI symptoms.

Conclusions

- **In this international, multi-center study, initial observations from the open-label cohort indicate that DMR was safely implemented in T2D subjects with a favorable safety and tolerability profile.**
- **DMR offers a safe and significant potential for the treatment of high unmet need metabolic diseases, including in patients with both T2D and NAFLD/NASH.**
- **Data from the randomized cohort is expected later this year.**

DISCLOSURES

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